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ORIGINAL ARTICLE

Incidence and risk factors of new-onset hypertrophic pachymeningitis in patients with anti-neutrophil antibody-associated vasculitis: using logistic regression and classification tree analysis

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Abstract

Objectives Hypertrophic pachymeningitis (HP) is a rare complication in patients with anti-neutrophil antibody-associated vasculitis (AAV); its clinical features, incidence, and risk factors remain unknown. We aimed to clarify the prevalence, clinical features, and factors associated with new-onset HP in patients with AAV.

Method A retrospective cohort study involving 93 patients with AAV was conducted. HP incidence between patients with granulomatosis with polyangiitis (GPA) and those with microscopic polyangiitis (MPA) was compared to investigate risk factors associated with HP. We performed only univariate analysis using logistic regression and classification tree (CART) analysis due to the small number of HP cases.

Results Among the 93 patients (76 with MPA and 17 with GPA), only 6 patients developed HP (1 with MPA, 5 with GPA) over an average observation period of 4 years; all patients who developed HP were positive for myeloperoxidase anti-neutrophil antibody. HP incidence was significantly higher in patients with GPA than in those with MPA (60.2 versus 3.3 persons per 1000 person-years, respectively, $P = 0.002$). The univariate analysis revealed that otitis media ($P < 0.001$) and sinusitis ($P = 0.014$) were associated with new-onset HP. Univariate CART analysis grouped the patients into patients with HP who have otitis media (33%) and patients with HP who have sinusitis (21%). The odds ratio of otitis media adjusted by age and first diagnosis of AAV was 38.1 (95% confidence interval, 3.08–331.4; $P = 0.004$).

Conclusions Although only in the univariate analysis, otitis media was the most discriminating factor to predict new-onset HP in patients with AAV.

Keywords Granulomatosis with polyangiitis · Hypertrophic pachymeningitis · Microscopic polyangiitis · Myeloperoxidase anti-neutrophil antibody · Otitis media · Proteinase 3 anti-neutrophil antibody

Introduction

Hypertrophic pachymeningitis (HP) is a rare clinical disorder caused by localized or diffuse thickening of the dura mater. The chief clinical manifestations of HP are headaches and multiple cranial neuropathies [1]. HP may be idiopathic or secondary to a number of conditions, such as autoimmune disease, infection, trauma, and malignancy. Recently, several studies, including many from Japan, have reported an association between anti-neutrophil cytoplasmic antibody (ANCA) and HP; the majority of individuals with HP in these studies were positive for myeloperoxidase-ANCA (MPO-ANCA) and were classified as patients with granulomatosis with polyangiitis (GPA) [2–12]. However, the incidence and risk factors of new-onset HP in patients with anti-neutrophil antibody-associated vasculitis (AAV) remain unclear. Hence, the aim of this study was to investigate the incidence of HP in patients with AAV. We also aimed to identify important risk factors for new-onset HP in this patient population by using classification and logistic regression tree (CART) analysis. CART analysis is a statistical method that divides the

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observations into subgroups using the factor that best separates those with and without the outcome. The results are displayed as a flow chart that can be easily understood. No previous study has shown the risk factors for HP in patients with AAV using CART analysis.

Materials and methods

Diagnostic criteria and clinical variables

This retrospective cohort study involved 93 patients with AAV who were recruited from Toranomon Hospital and Toranomon Hospital Kajigaya between January 1, 2004, and September 30, 2015. We reviewed medical records and compared the incidence of HP in patients with MPA to that in patients with GPA to investigate the risk factors associated with HP development among patients with AAV.

The diagnostic criteria for HP were as follows: (1) the presence of a headache or cranial neuropathies, (2) the presence of thickened or abnormal enhancement of the dura mater as determined from gadolinium magnetic resonance imaging (MRI) T1 sequences, and (3) the exclusion of other causes of HP such as tuberculosis, syphilis, malignancy, or intracranial hypotension. Dural biopsies were not performed in any patient, although an autopsy in one patient revealed fibrous thickening of the dura mater. Cerebrospinal fluid (CSF) was analyzed for pressure, cell count, protein, immunoglobulin G (IgG) index, and interleukin 6 (IL-6).

Diagnosis and classification of AAV were made according to Watt's algorithm (13) based on the following organ involvement definitions. Interstitial pneumonia was defined based on radiology or computed tomography (CT) evidence of an interstitial pattern. Alveolar hemorrhage was defined based on CT evidence of ground glass opacity and bronchoalveolar lavage evidence of an increase in red blood cells and hemosiderin deposits in the alveolar macrophages. Kidney involvement was defined as rapid progressive glomerular nephritis and/or the presence of a crescent formation or necrosis on kidney biopsy. Chronic otitis media, sinusitis, and mastoiditis lasting more than 3 months were regarded as surrogate markers of upper airway involvement among patients with GPA. ANCA testing was performed via indirect immunofluorescence microscopy prior to December 1996, enzyme-linked immunosorbent assay between January 1997 and November 2012, and chemiluminescent enzyme immunoassay after December 2012.

Follow-up MRI was performed in patients with worsening symptoms of headaches or cranial neuropathies and elevated C-reactive protein (CRP). Relapse was defined as the deterioration of MRI findings with or without the development of clinical symptoms. The study was carried out in compliance with the Helsinki declaration and approved by the Ethics Committee of Toranomon Hospital (Ethical board approval number 1093).

Statistical analysis

Data are presented as the mean and standard deviation (SD) for continuous variables and proportions for categorical variables. We classified patients with AAV based on the onset of AAV (first diagnosis of AAV) and the last date of observation (last diagnosis of AAV) because AAV diagnoses changed during the observation period for some patients. We used CART analysis. CART identifies the smallest set of the best performing clinical characteristics or markers and identifies values for each characteristic that maximize the separation between patients with HP and those without HP. We performed only univariate analysis by using a logistic CART because of the small number of HP cases. The cumulative incidence of new-onset HP was calculated in a competing risk model, in which death from any cause was considered a competing risk. The time to new-onset HP was calculated from the date of the first AAV diagnosis. For patients diagnosed before January 1, 2004, we set the date of the AAV diagnosis as January 1, 2004. We calculated the adjusted odds ratio by correcting the odds ratio with the lowest number of confounding variables because of the small number of HP cases.

All statistical analyses were conducted using STATA SE13, and $P < 0.05$ was considered statistically significant.

Results

Clinical characteristics of the six patients with AAV and HP

Among the 93 patients, 6 patients developed HP during the observation period. The clinical characteristics of the 6 patients (2 male and 4 female patients) are reported in Table 1. The median age of these patients was 74 years; they were followed for an average of 7.8 (4–22) years and were all positive for MPO-ANCA and negative for PR3-ANCA. The median observation period from the onset of AAV to the new-onset HP was 37 months (0–175). Two patients were diagnosed with HP at the initial clinical episode of vasculitis whereas 4 patients were diagnosed during steroid taper due to remission in AAV.

Four patients reported headaches at the HP diagnosis and the other two patients reported headaches at the time of HP recurrence. Four patients presented with cranial nerve palsy (II-V, VII-XII); cranial nerve II palsy was the most frequent presentation. CSF IgG index levels were increased in all six patients; CSF IL-6, which was measured in only two patients, was increased in both patients. One patient exhibited high opening pressure; one patient, pleocytosis; and one patient, increased CSF protein. Serum CRP was elevated in all six patients (9.6 ± 4.6 mg/dL).

Table 1 Clinical characteristics of patients with AAV and HP

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age/sex	63/male	77female	53/male	83/female	70/female	64/female
Duration from the onset of AAV to the onset of HP	Initial manifestation	Initial manifestation	175 months	29 months	37 months	47 months
Clinical manifestation						
Headache	+	+	+	+	+	+
Cranial neuropathy	II	VII-XII	II	IIIIIIVV	VII	–
Laboratory data						
MPO-ANCA (EU)	71	190	13	< 10	14.8	1
CRP (mg/dL)	16.6	15.2	6.5	5.3	2.6	10.3
Site of thickening of the dura mater in MRI	Bilateral, diffuse	Right tentorium cerebelli	Bilateral, diffuse	Left cavernous sinus	Right dominant	Bilateral, frontal
CSF						
Pressure (mmHg)	–	130	350	200	270	180
Cell count (/μL)	0	14	71	2	3	22
Protein (mg/dL)	38	18	258	26	125	66
IgG index (< 0.73)	2.15	1.64	5.02	1.53	0.76	0.86
IL-6 (pg/mL)	–	–	–	–	102	8.4
Other organ involvements						
Kidney	+	+	+	+	+	+
Lung	–	–	–	+	+	+
Otitis media	–	+	+	+	+	–
Sinusitis	+	+	–	+	–	–
Mastoiditis	–	+	–	+	–	–
Diagnosis						
Initial diagnosis	MPA	MPA	MPA	GPA	GPA	MPA
Final diagnosis	GPA	GPA	GPA	GPA	GPA	MPA
BVAS at the onset of HP	21	27	5	17	17	10
Treatment						
At the onset of HP	None	None	PSL 3.5mg + CyA	PSL 5mg	PSL 14mg	PSL 11mg + Mz
After the onset of HP	mPSL pulse + PSL + CyA	mPSL pulse + PSL	mPSL pulse+ PSL + CyA	mPSL pulse + PSL	mPSL pulse + PSL	mPSL pulse + PSL + Mz
Recurrence (months)	39	–	–	10	11	9
Treatment at the recurrence	PSL 10mg + Mz	–	–	PSL 16mg	PSL 10mg	PSL 20mg + Mz
MPO-ANCA status at the time of recurrence	Negative	–	–	Negative	Elevated	Elevated

MPO-ANCA was elevated in two patients (cases 1 and 2; 71 EU and 190 EU, respectively); both patients presented with HP at AAV onset. However, AAV was stable in the other four patients that presented with HP; MPO-ANCA was slightly elevated in two of these patients (13 and 14.8 EU, respectively) and negative in the two other patients.

At the onset of HP, except for two patients that developed HP as initial manifestation of AAV (cases1 and 2), two patients were treated with oral prednisolone only, one patient with oral prednisolone and cyclosporine, and one patient with prednisolone and mizoribine. All the patients received methylprednisolone pulse therapy as first-line treatment for the HP. Except in cases 1 and 4, in which both patients experienced vision loss; the headaches and cranial nerve palsies improved in all six cases.

HP recurred in four patients following a reduction in prednisolone dosage. All four patients reported headaches. Two patients were MPO-ANCA negative at the time of HP recurrence. MPO-ANCA was slightly elevated in two patients with relapsing AAV; one patient presented with alveolar hemorrhage, and the other presented with otitis media and mastoiditis.

Five patients exhibited kidney involvement as an initial manifestation of AAV. Two patients (cases 1 and 2) were

diagnosed with HP concomitant with new-onset kidney involvement as the first manifestation of AAV. The other three patients were diagnosed with HP several years after the onset of AAV.

We performed a renal biopsy in five patients to diagnose the vasculitis. Table 1 reports the clinical features of renal biopsy. Biopsy confirmed vasculitis in all five patients. A crescent formation was observed in the glomeruli in five patients (diffuse in 1 patient and focal in 4 patients), fibrinoid necrosis was observed in the glomeruli in two patients, and interlobular artery necrosis was observed in two patients. Except for microhematuria or mildly elevated levels of N-acetylglucosaminidase, α1-macroglobulin, and β2-microglobulin in the urine, three patients exhibited normal renal function. One patient (case 6) had suspected glomerulonephritis, but the patient refused a renal biopsy.

Three patients had interstitial pneumonia prior to HP onset. One patient developed alveolar hemorrhage at the time of HP recurrence.

Among the six patients with HP, four patients exhibited otitis media with effusion, two exhibited mastoiditis, and three exhibited chronic sinusitis prior to HP diagnosis. One patient (case 1) presented with sinusitis 3 years after HP diagnosis. We performed nasal mucosa biopsies in four patients and paranasal sinus mucosa biopsy in one case, but no granuloma or vasculitis was found.

According to Watt's algorithm, two of the six patients with HP were diagnosed with GPA and the four other patients were diagnosed with MPA at the time of AAV onset. However, among the four patients with MPA, three patients presented with the surrogate markers of GPA during the observation period; thus, their diagnosis changed to GPA. Hence, only one patient had MPA and the other five patients, GPA, at the last diagnosis (Table 1). Biopsies did not reveal granuloma in any of the five patients with GPA.

Baseline characteristics of patients

Among the 93 patients, 83 cases (89.2%) were classified as MPA and 10 cases (10.8%) as GPA at AAV onset according to Watt's algorithm. However, seven patients with MPA appeared to exhibit the surrogate markers of GPA during the observation period, and their diagnosis was changed from MPA to GPA. Thus, 76 cases were classified as MPA (81.7%) and 17 cases as GPA (18.3%) at the end of the observation period (Fig. 1). We report the baseline characteristics of the patients with AAV including 6 HP cases and 87 no HP cases in Table 2. In all the patients with AAV, the mean observation period was 4.2 years; mean age, 69 ± 13 years; and 32.3% of the patients were male.

Median observation periods were 6.3 and 4.0 years in patients with HP and with no HP, respectively. The incidences of sinusitis, otitis media, and mastoiditis were higher in patients with HP compared to patients with no HP (50.0% versus 12.6%, 66.7% versus 5.7%, and 50.0% versus 2.3%, respectively).

Incidence rate of new-onset HP in patients with AAV

Table 3 shows the incidence rate (per 1000 person-years) of new-onset HP in patients with AAV. We classified the diagnosis of AAV both at the onset of AAV (first diagnosis of AAV) and at the last date of observation (last diagnosis of AAV). During the median follow-up period of 3.6 years, six patients had new-onset HP at the last date of observation. At the first diagnosis, four of the patients had been diagnosed with MPA and two patients with GPA; however, at the last diagnosis, one patient was diagnosed with MPA and five patients with GPA. Four patients experience HP relapse during the observation period; at first diagnosis, three patients had been classified under MPA and one patient under GPA; however, at the last diagnosis, one patient was classified under MPA and three patients under GPA. The incidence rate of new-onset HP

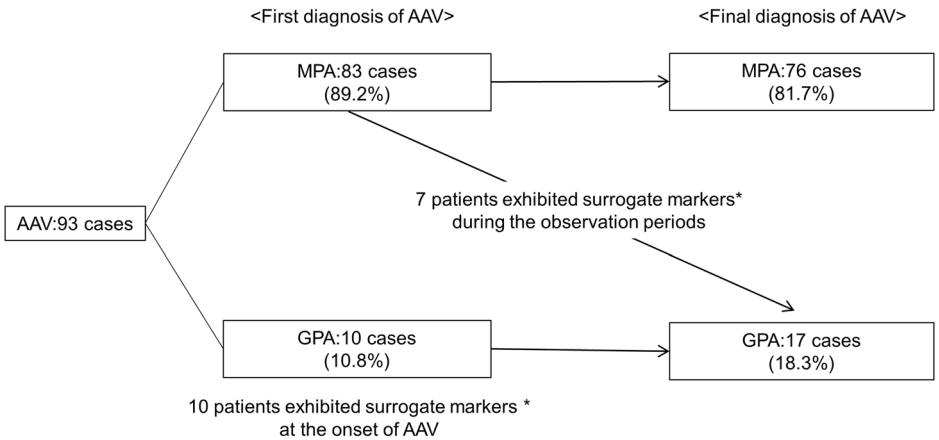

Fig. 1 Summary of the appearance of surrogate markers of granulomatosis with polyangiitis (GPA) during the observation periods

*Chronic otitis media, sinusitis, and mastoiditis lasting more than 3 months are regarded as surrogate markers of GPA

Table 2 Baseline characteristics of patients with or without HP

	Overall $n = 93$	HP+ $n = 6$	HP− $n = 87$
Male sex, *n* (%)	30 (32.3%)	2 (33.3%)	28 (32.2%)
Age at the time of diagnosis of vasculitis	69 ± 13	67 ± 12	67 ± 11
ANCA type			
MPO-ANCA positive	79 (84.9%)	5 (83.3%)	74 (85.0%)
PR3-ANCA positive	7 (7.5%)	0 (0.0%)	7 (8.0%)
Double positives	7 (7.5%)	1 (16.7%)	6 (6.9%)
Observation periods (year)	4.2 ± 3.6	6.3 ± 3.2	4.0 ± 3.6
Involved organs			
Kidney	82 (88.2%)	5 (83.3%)	77 (88.5%)
Lung	50 (53.8%)	3 (50.0%)	47 (54.0%)
Sinusitis	14 (15.1%)	3 (50.0%)	11 (12.6%)
Otitis media	9 (9.7%)	4 (66.7%)	5 (5.7%)
Mastoiditis	5 (5.4%)	3 (50.0%)	2 (2.3%)
First diagnosis of GPA	10 (10.8%)	2 (33.3%)	8 (9.2%)
Last diagnosis of GPA	17 (18.3%)	5 (83.3%)	12 (13.8%)

was significantly higher among patients with GPA compared to patients with MPA at both the first and last AAV diagnoses (first diagnosis: 512.8 versus 11.4 persons per 1000 person-years, $P = 0.002$; last diagnosis: 60.2 versus 3.3 persons per 1000 person-years, $P = 0.002$).

CART analysis to determine risk factors for new-onset HP in patients with AAV

To determine risk factors for new-onset HP in patients with AAV, we could perform only univariate CART analysis because the number of patients with HP was small.

Figure 2 shows the results of the CART analysis. The proportion of AAV patients in each subgroup who presented with HP is shown. New-onset HP was significantly associated with the appearance of GPA surrogate markers. Univariate CART analysis splits patients into groups based on the percentage with HP: 33% HP with otitis media, 21% HP with sinusitis and otitis media ($P < 0.001$), and sinusitis ($P = 0.014$) were associated with new-onset HP, and otitis media was the most discriminating factor to predict new-onset HP in patients with AAV. The variables which did not show significance in the CART analysis including male sex, age over 75 years, ANCA typing, and classification at the onset of AAV involved other organs (kidney and lung) and were also not significantly associated with the onset of HP in the logistic analysis.

We also calculated the odds ratio of otitis media adjusted by correcting with the lowest number of confounding variables because of the small number of HP cases, and the adjusted odds ratio of otitis media adjusted by age and the first diagnosis of AAV was 38.1 (95% confidence interval 3.08–331.4: $P = 0.004$) (Table 4).

Discussion

We experienced six cases of HP in patients with AAV, which was previously thought to be a rare complication. Furthermore, we analyzed the incidence of new-onset HP in patients with AAV and revealed the risk factors for new-onset HP in patients with AAV for the first time. The main findings are as follows: (1) the incidence of new-onset HP was

Table 3 Incidence (per 1000 person-years) of new-onset HP in patients with MPA and GPA at the first and last diagnosis of AAV

Type of vasculitis	Number of patients with new-onset HP	Total HP events	Person-years	Incidence rate of New-onset HP (1000 person-years)	*P* value
First diagnosis of AAV					
MPA	4	7	351.3	11.4	0.002
GPA	2	3	3.9	512.8	
Last diagnosis of AAV					
MPA	1	2	306.0	3.3	0.002
GPA	5	8	83.0	60.2	

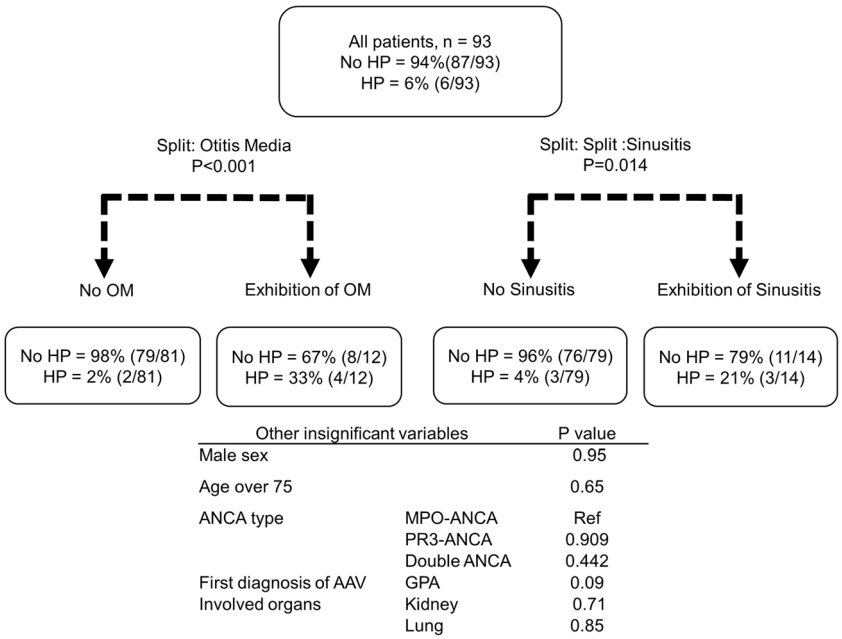

Fig. 2 Classification tree to predict new-onset HP in patients with AAV using univariate analysis. The proportion of patients with AAV in each subgroup who had HP

significantly higher among patients with GPA than in patients with MPA, based on the last diagnosis of AAV (60.2 versus 3.3 persons per 1000 person-years) and (2) the appearance of surrogate markers was a significant risk factor for predicting the onset of HP (adjusted odds ratio, 38.1).

Recently, Yonekawa et al. reported a Japanese epidemiological survey of HP [2]. They showed that the crude HP prevalence in Japan was 0.949 per 100,000 individuals and that 34% of patients with HP were ANCA-positive (i.e., ANCA-related HP). They also reported that 27.7% of patients were MPO-ANCA positive and that 12.6% of all the patients with HP were PR3-ANCA positive. However, they did not mention the classification of AAV precisely. Yokoseki et al. reported that among 21 cases of ANCA-positive HP, PR3-ANCA positivity was found in only 22.2% of cases, and MPO-ANCA positivity was found in up to 77.8% of cases, although most of the cases were classified as GPA [3]. MPA is extremely rare among patients with MPO-ANCA-positive HP; only eight cases have been reported, including our case, and all cases were reported from Japan [10–12].

The prevalence of HP in patients with GPA was 0–3.3% in previous reports [4, 13–15]; however, only a few studies have comprehensively assessed the incidence of HP in patients with AAV, especially among those with MPA. To the best of our knowledge, this is the first analysis that compares the incidence of HP between patients with MPA and patients with GPA.

The majority of patients with ANCA-related HP were MPO-ANCA positive, diagnosed with GPA, and reported from Japan. The epidemiological manifestations of AAV differ across geographic regions. In a study, the prevalence of GPA and MPA in AAV was significantly different between Japan and the United Kingdom (UK) [16]. Moreover, while MPA was the predominant subtype in Japan (83%), GPA was more predominant in the UK (66%). The ratio of MPO-positive patients was significantly higher in Japan than in the UK (83.7% and 30.0%, respectively); however, there were significantly fewer PR3-positive patients in Japan than in the UK (7.0% and 58.0%, respectively). Moreover, MPO-ANCA-associated cases and PR3-ANCA-associated cases constituted up to 91.8% and 6.1%, respectively, of patients with MPA and 22.7% and 71.1%, respectively, of patients with GPA in Japan [17]. The prevalence of MPA and GPA within each ANCA phenotype may be different between patients with AAV with and with no HP.

Our study had several strengths that are noteworthy. This is the first study to use CART analysis for patients with HP. The univariate analysis using CART analysis revealed that the appearances of surrogate marker, otitis media, and sinusitis were

Table 4 The odds ratio of surrogate markers adjusted by age and first diagnosis of AAV

Variables		Odds ratio	(95% CI)	*P* value
Age over 75 years		0.97	(0.90–1.05)	0.43
First diagnosis of AAV	MPA	Ref		
	GPA	0.49	(0.04–5.47)	0.56
Involved organs	Otitis media	38.1	(3.08–331.4)	0.004

significant risk factors for predicting the onset of HP. Although the number of patients who developed HP in our study was too small for multivariate analysis, we calculated the adjusted odds ratio of otitis media adjusting for age (over 75 years old) and the first diagnosis of AAV (adjusted OR, 38.1). This finding is consistent with the results of the study by Yonekawa et al., in which it was reported that patients with ANCA-related HP exhibited a higher frequency of otological symptoms compared with those with idiopathic HP [2]. Among 17 cases of MPO-ANCA-positive HP in that study, 14 cases (82%) were classified as GPA. Furthermore, patients with MPO-ANCA-positive HP exhibited a higher prevalence of surrogate markers for GPA, including chronic sinusitis (29%), otitis media (65%), or mastoiditis (47%); however, no patient exhibited granuloma [3]. These findings are also consistent with our study. Furthermore, our data indicate that the appearance of surrogate markers of upper airway involvement is a more important risk factor for predicting the onset of HP than the classification of AAV. All the patients who were diagnosed with GPA at the last date of observation exhibited the surrogate markers of upper airway involvement. We investigated the incidence of HP in the ANCA cohort, and this is the first analysis that compares the incidence of HP between patients with MPA and patients with GPA. To the best of our knowledge, this analysis is the first to investigate the risk factors of new-onset HP in patients with AAV in a longitudinal study.

Importantly, at the onset of AAV, ten patients in our AAV cohort had the surrogate markers. However, seven patients who did not have surrogate markers at AAV onset developed the markers during the observation period, and the classification of AAV changed from MPA to GPA. Among the seven patients, three developed HP.

Thus, it is important to assess patients carefully for the appearance of surrogate markers even in patients with MPA.

There were some limitations to this study. First, due to the retrospective cohort design, our findings are subject to unmeasured confounding factors that may have influenced the results. Second, there is potential for selection bias. Third, our study population was small and was derived from two facilities. Fourth, dura mater histology was performed in only one case. Fifth, because the incidence of HP is rare, we did not perform multivariate analysis.

Further studies are necessary to clarify the incidence and risk factors of HP in patients with AAV.

Conclusion

The incidence rate of new-onset HP was significantly higher in patients with GPA than in patients with MPA. The appearances of otitis media and sinusitis were significant risk factors for predicting the onset of HP. This finding emphasizes the importance of assessing the appearance of surrogate markers of upper airway tract involvement to predict the incidence of HP in patients with AAV.

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Author's contribution

A.I. designed the study, performed data analysis, and wrote the manuscript; N.S. designed the study, performed data analysis, and critically revised the manuscript; M.K., R.H., E.H., Y.U., and K.T. provided clinical care and critically revised the manuscript.

Compliance with ethical standards

Disclosures None.

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